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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HAYES, ROBERT CLINTON	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,499	BAKER ET AL.	
	Examiner	Art Unit	
	Robert C. Hayes, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-35 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-35 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/16/05;2/16/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *1xreference*.

DETAILED ACTION

Response to Amendment

1. The amendment filed on 1/16/05 has been entered.

2. The rejection of claims 28-33, 36-37 & 39-40 under 35 U.S.C. 112, second paragraph, as being indefinite for what constitutes a extracellular domain is withdrawn due to the cancellation or amendment of the claims.

3. The rejection of claims 28-33, 36-37 & 39 under 35 U.S.C. 102(a) as being anticipated by Koehrer et al. (1999) is withdrawn due to the cancellation or amendment of the claims.

4. Applicant's arguments filed 1/16/05 have been fully considered but they are not deemed to be persuasive.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. The information disclosure statement filed 1/16/05 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; *and all other information or that portion which caused it to be listed.* The information has been considered to the extent

possible. However, no direct comparisons with the listed sequences and that claimed have been provided for reasonable and complete consideration by the Examiner. Thus, they will not be printed on the face of the patent issuing from this application, because they do not represent a full disclosure of what these crossed out sequences actually represent. Nor has any copies of any referenced WIPO or EP patents been submitted for full consideration on a properly executed PTO-1449.

Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP 609 C(1) & B(3).

7. Claims 28-35 & 38-40 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility, for the reasons made of record in Paper No: 20040913, and as follows.

Applicant's arguments on pages 9-17 of the response have been fully considered but are not found to be persuasive because the specification does not identify a single "reasonable use" for the claimed polypeptides of the instant invention. In other words, the claimed functional use of DNA for detecting colon tumors is not equivalent to identifying a use for the claimed polypeptides. The Goddard, Polakis and Ashkenazi Declarations under 37 CFR 1.132, all filed 16 January 2005, are further insufficient to overcome the rejection of claims 28-35 & 38-40 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons:

The Goddard Declaration is not deemed persuasive, because the issue is not the accuracy

of the Taq DNA polymerase assay wherein the Taqman PCR technique is sensitive enough to detect "at least [a] 2-fold increase in gene copy number relative to control... [and wherein such an increase] is significant and useful... as a marker for the diagnosis of cancer...". In contrast, "increase in gene copy number" (i.e., DNA data) is not equivalent to increased polypeptide levels.

The Ashkenazi Declaration is not deemed persuasive, because the issue is not that "even when amplification of a cancer marker gene does not result in significant over-expression of the gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment". In contrast, the issue is that the instant specification provides no information regarding increased PRO1788 polypeptide levels in tumor samples relevant to normal samples, and that there is no evidence as to whether the gene products (such as the polypeptide) are over-expressed or not. Only gene amplification data (i.e., DNA data) is presented in the instant specification.

The Polakis Declaration is not deemed persuasive, because the issue is not that approximately 200 gene transcripts (i.e., mRNA) have been identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells, or that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. The issue is that the instant specification provides no information regarding increased mRNA levels of PRO1788 in tumor samples relevant to normal samples. Only gene amplification (DNA) data is presented within the instant specification. Importantly, it is noted that this declaration further does not provide data for the Examiner to

independently draw any conclusions. Only Dr. Polakis' conclusions/ "opinions" are provided in this declaration. Likewise, no evidence is presented to support Dr. Polakis' statement that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide." In contrast, the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels (i.e., mRNA) between normal and cancerous tissue. For example, Hu et al. (2003) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level (i.e., mRNA) between breast cancer samples and normal samples in a microarray (pg. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level (i.e., mRNA), there was a strong and significant correlation between expression level and a published role in the disease (see pgs. 411-412). Thus, no such dogma is universally recognized within the art; especially as it relates to small changes in gene expression being predictive of cancer. Nevertheless, gene amplification (i.e., as it relates to the instant specification) is not equivalent to gene expression (i.e., mRNA), which is not the same as polypeptide data (i.e., as claimed).

Applicant argues that "[t]he Examiner has not shown whether the lack or correlation observed for the WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule", as it relates to Pennica et al. However, it is noted that Applicant's assertions that "a correlation between DNA amplification and over-expression of polypeptide **was observed** in the case of WISP-1" is a clear misrepresentation of the teachings of Pennica, where no "polypeptide" levels were assayed in Pennica. In other words, mRNA is not protein.

Applicant argues that "Konopka does not disclose any generalized teaching about the correlation between protein expression and gene amplification", and "pertains... to merely **one** gene, the *abl* gene". However, Konopka et al. was cited as evidence showing a lack of correlation between gene amplification and increased polypeptide levels.

Applicant then argues that "the Haynes data meets the 'more likely than not standard' and shows that a positive correlation exists between mRNA and protein", and therefore "the Examiner's rejection is based on a misrepresentation of the data presented in Haynes et al." In contrast to Applicant's assertions, Pennica et al. was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Konopka et al. was cited as evidence showing lack of correlation between gene (DNA) amplification and increased polypeptide levels. Haynes et al. was cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as **40-fold** or even **50-fold** were not uncommon (pg. 1863). Therefore, no direct correlation between gene amplification and increased polypeptide levels exists, no dogma exists between mRNA and polypeptide levels (for which neither are disclosed within the instant specification for PRO1788), and no misrepresentation exists.

Thus, the issue becomes that the specification provides data showing a very small increase in **DNA** copy number of approximately **2-fold** in a few tumor samples for PRO1788. The specification fails to provide any evidence on whether or not the PRO1788 **mRNA** or **polypeptide** levels are also increased in these tumor samples. Because the instant claims are directed to PRO1788 **polypeptide**, it is imperative to find evidence in the relevant scientific art

as to whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased in mRNA and subsequent polypeptide levels. Given how small the DNA copy number of PRO1788 increased, and the evidence provided by Haynes et al., Pennica et al. and Konopka et al., it is clear that one skilled in the art would not assume that a small increase in gene (DNA) copy number would reasonably correlate with significantly increased mRNA or polypeptide levels, and therefore, "more likely than not" no generalized correlation exists between gene (DNA) amplification and increased polypeptide levels, based on the teachings of Haynes et al., Pennica et al. and Konopka et al., and for the reasons previously made of record.

Lastly, Applicant refers to three additional articles by Ornfoft et al., Hyman et al. and Pollack et al. as providing evidence that gene amplification *generally* results in elevated levels of the encoded polypeptide, which appears to contradict their previous position concerning generalizing the teachings of Konopka discussed on the previous page. Applicant characterizes Ornfoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. In contrast, Ornfoft et al. looked at increased DNA content over large regions of chromosomes and compared that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Ornfoft et al. do not look at gene

amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual PRO genes, which may or may not be in a chromosomal region that is highly amplified. Ornfoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (e.g., see pg. 40). Nevertheless, this analysis was not done for PRO1788 as discussed in the instant specification. In other words, it is not clear whether or not PRO1788 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Ornfoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. cannot support the establishment of utility for the claimed polypeptides. Likewise, Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (pg. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. cannot support the establishment of utility for the claimed invention. Thus, Applicant's conclusion that these references support their contention that "[i]n a vast majority of amplified genes, the teachings of the art, as exemplified by Ornfoft et al., Hyman et al. Pollack et al.... overwhelmingly show that gene amplification influences gene expression at the mRNA **and protein levels** [emphasis added]" is a clear mischaracterization of the teachings of Ornfoft et al., Hyman et al. Pollack et al. Accordingly, the specification's assertion that the claimed PRO1788 polypeptides has utility in the fields of cancer diagnostics and cancer therapeutics is not substantial, by definition, because further experimentation is clearly required to establish such a use for the claimed PRO1788 polypeptides, for the reasons discussed above.

In summary, the instant specification provides a mere invitation to experiment for establishing a specific and substantial use for the claimed polypeptides, which does not reasonably extrapolate to a readily available utility. Moreover, the PRO1788 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. The specification merely demonstrates that the PRO1788 nucleic acid was amplified in some cancers, to a minor degree (i.e., " at least 2-fold increase"). No mutation or translocation of PRO1788 has been associated with any type of cancer versus normal tissue. It is not known whether PRO1788 is expressed in corresponding normal tissues, and what the relative levels of expression are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO1788 is amplified in a variety of samples, including some normal tissues, and invites the artisan to determine the significance of this increase. One cannot determine from the data in the specification whether the observed "amplification" of nucleic acid is "more likely than not" to increase in chromosomal copy number, or alternatively due to an increase in transcription rates. Therefore, the specification merely presents an invitation for others to experiment and discover a use for the claimed polypeptides of the instant invention.

In conclusion, for the reasons discussed above and previously made of record, because the proposed use of the PRO1788 polypeptides are simply starting points for further research and investigation into potential practical uses of the polypeptides, the instant claims have no specific nor substantial utility, consistent with that held by the court in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966):

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

8. Claims 28-35 & 38-40 stand also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for the reasons made of record in Paper No: 20040913.

9. Claims 28-33 & 39-40 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons made of record in Paper No: 20040913, and as follows.

In contrast to Applicants' assertions on page 19 of the response, a recitation related to DNA does not reasonably constitute a "functional limitation" for the claimed polypeptides. In other words, as previously made of record, the specification has not described or shown possession of all polypeptides 80-99% homologous to SEQ ID NO: 397, which retain the function of SEQ ID NO: 397, if later discovered. Nor have Applicants described a representative

number of species that have 80-99% homology to SEQ ID NO: 397, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 397.

As previously made of record, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, *as of the filing date sought*, he or she was in possession *of the claimed invention*". "The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed* [emphasis added]". Therefore, Applicants' arguments are not persuasive.

Second, page 301 of the specification specifically states that "[t]he PRO polypeptides described herein *may be isolated from a variety of sources*, such as from human tissue types *or from another source*... [emphasis added]" . In contrast, as previously made of record, the sole single *human* polypeptide species described is PRO1788 of SEQ ID NO: 397. No written description is provided in the specification for any **other** species of PRO1788 molecules, in which disclosure of a single **"human"** polypeptide sequence (*which the claims are not limited toward*) does not reasonably constitute "the claimed genus of polypeptides".

Analogous to the situation decided in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), "an adequate written description of a DNA [product] requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself". *Fiddes v. Baird*, 30 USPQ2d 1481, 1483 (1993) held that claims directed to mammalian FGFs were found unpatentable due to lack of written description for the broad class, in which the specification had provided an adequate description of only the bovine sequence. Similarly, only the single *human* polypeptide species of SEQ ID NO: 397 has been described in the instant specification.

Accordingly, the court held in *Univ. California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) that:

"One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is".

and that:

"A description of a genus of cDNAs [products] may be achieved by means of a recitation of a representative number of cDNAs [products], *defined by nucleotide sequence*, failing in the scope of the genus or of a recitation of structural features common to the members of the genus, *which features constitute a substantial portion of the genus* [emphasis added]. This is analogous to enablement of a genus under 112, [first paragraph], by showing the enablement of a representative number of species within the genus. See Angstadt, 537 F.2d at 502-03, 190 USPQ at 218".

In contrast, an invitation for others to discover a representative number of species with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics has not reasonably been provided within the instant specification. Thus, Applicant was not reasonably in possession of the "claimed genus of polypeptides", and for the reasons previously made of record. See again MPEP 2163.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961. The fax phone number for this Group is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert C. Hayes, Ph.D.
April 28, 2005

ROBERT C. HAYES, PH.D.
PATENT EXAMINER